pattern may not be as strongly influenced by a hormonal effect on channel function.

A genome-wide association study recently suggested an intriguing associated locus near the *KCND3* (Kv4.3) gene, which encodes a subunit of the Ito channel (5). The association was not significant genome-wide, and it did not replicate in other study populations.

Nevertheless, the biological plausibility of Ito channel involvement in ER ECG formation seems to be more than a coincidence. Future studies in this field should perhaps focus on finding genetic variants of the ER ECG pattern followed by a horizontal/downsloping ST-segment, which could highlight better the genetic background of the ER syndrome.

The presence of an inferolateral ER ECG is affected by testosterone level, which probably explains the male predominance and the decline with aging of this ECG pattern. Furthermore, the ER ECG pattern with a rapidly ascending ST-segment seems to be the pattern most closely associated with testosterone level.

***M. Juhani Junttila, MD†**
Jani T. Tikkanen, MD†
Kimmo Porthan, MD‡
Lasse Oikarinen, MD‡
Antti Jula, MD§
Tuomas Kenttä, PhD†
Veikko Salomaa, MD§
Heikki V. Huikuri, MD†

*Department of Internal Medicine
Institute of Clinical Medicine
University of Oulu
P.O. Box 5000
FI-90014, Oulu
Finland
E-mail: juhani.junttila@oulu.fi

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From the †Department of Internal Medicine, Institute of Clinical Medicine, University of Oulu and Oulu University Central Hospital, Oulu, Finland; ‡Division of Cardiology, Department of Medicine, Helsinki University Central Hospital, Helsinki, Finland; and the §National Institute for Health and Welfare, Turku and Helsinki, Finland.

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Letters to the Editor

Higher N-Terminal Pro–B-Type Natriuretic Peptide May Be Related to Very Different Conditions

We read the paper by Hijazi et al. (1) with interest. The authors investigated the incremental value of measuring N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels in addition to established risk factors (including the CHA_2DS_2VASc [heart failure, hypertension, age 75 years and older, diabetes, and previous stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category (female sex, respectively)] score) for the prediction of cardiovascular and bleeding events. They concluded that NT-proBNP levels are often elevated in atrial fibrillation (AF) and independently associated with an increased risk for stroke and mortality. NT-proBNP improves risk stratification beyond the CHA_2DS_2VASc score and might be a novel tool for improved stroke prediction in AF. The efficacy of apixaban compared with warfarin was independent of the NT-proBNP level.

Although most widely used as a marker of systolic heart failure, elevated NT-proBNP has been reported in patients with diastolic dysfunction (2). Therefore, it is important to determine diastolic and systolic function by echocardiography. Performing echocardiography also is important for measurement of pulmonary artery pressure. Pulmonary arterial hypertension is common with rheumatic diseases, and NT-proBNP levels may be a result of the increase in pulmonary pressure (3). On the other hand, high levels of NT-proBNP can be seen in many conditions that increase cardiac output and cardiac stress, such as sepsis, cirrhosis, and hyperthyroidism (4). That is why determination of liver test results and thyroid hormone profile may reveal stronger results in such a study.

NT-proBNP is an important prognostic factor for cardiovascular diseases; however, besides cardiac diseases, elevated NT-proBNP levels may be seen in several diseases. A prominent disease with elevated NT-proBNP is a respiratory system disease, such as chronic obstructive pulmonary disease, pulmonary embolism, and interstitial lung disease, in which B-type natriuretic peptide levels are elevated in response to the pressure of the right side of the heart (5). In addition, cor pulmonale, secondary pulmonary hypertension, or hypoxemia may represent important stimuli for the release of NT-proBNP from the right side of the heart. Given that hypoxemia alone is a risk factor for the development of AF, respiratory system disorders should not be ignored in such a study.

Furthermore, Hijazi et al. (1) used the Cockcroft-Gault (CG) equation to determine the glomerular filtration rate (GFR). However, the CG equation may measure a lower GFR in younger age groups, and GFR can be higher in older individuals. Although the Chronic Kidney Disease Epidemiology Collaboration recently published an equation for GFR using the same variables (serum creatinine level, age, sex, and race) as the CG equation, the Chronic Kidney Disease Epidemiology Collaboration equation more accurately categorized individuals with respect to long-term clinical risk compared with the CG equation (6).

Elevated NT-proBNP independently predicts all-cause mortality and morbidity of patients with AF. However, higher NT-proBNP levels may be associated with different conditions, and the pivotal roles of those factors evaluate further large-scale, prospective randomized clinical trials. In addition, measuring not only NT pro-BNP, but also troponin T and I (7), is an easy method to assess increased risk for stroke and mortality in patients with AF. These markers might be useful in clinical practice. Finally, one should keep in mind that NT-proBNP alone without other predictive markers may not give exact information to clinicians about the prognostic indication of patients; thus, NT-proBNP should be evaluated along with other serum mortality predictive markers.

*Sevket Balta, MD
Sait Demirkol, MD
Mehmet Aydogan, MD
Turgay Celik, MD

*Department of Cardiology
Gulhane School of Medicine
Tevfik Saglam St.
Etlik-Ankara 06018
Turkey
E-mail: drsevketb@gmail.com

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Reply

Higher N-Terminal Pro–B-Type Natriuretic Peptide May Be Related to Very Different Conditions

We thank Dr. Balta and colleagues for their comments on our article concerning the use of N-terminal pro B-type natriuretic peptide (NT-proBNP) for atrial fibrillation (AF) in the ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation) trial (1). Of the 18,201 patients with AF in the ARISTOTLE trial, 14,892 comprised the population in whom baseline NT-proBNP plasma samples were analyzed. The results showed that NT-proBNP was strongly and independently related to stroke, cardiovascular events, and mortality.

As Dr. Balta and colleagues point out, several states may affect NT-proBNP levels (2,3). However, it is important to view this in the context of the current study. Reversible causes of AF (e.g., infection, sepsis acute lung disease exacerbation, and thyrotoxicosis) were excluded, and patients were generally stable at the time of enrollment with regard to other medical illnesses (4). Moreover, adjustments were performed with Cox proportional hazards models for established risk factors, including heart failure, renal function, and biomarkers of myocardial damage measured with troponin. It is true that a large number of factors, including lung disease, will contribute to elevation of NT-proBNP, and some of these no doubt contributed to the pathophysiologic link of NT-proBNP elevation and clinical events. Irrespective of the mechanism, however, what we showed was that the information obtained from NT-proBNP levels, in addition to the clinical risk factors, provided independent prognostic information in the population with AF.

It is well known that various equations used to estimate renal function have their strengths and weaknesses, and we can reassure Dr. Balta and colleagues that our findings were not dependent on the Cockcroft-Gault formula because we used cystatin C as the biomarker to reflect renal function. This newer marker of renal function does not depend on age for estimating the glomerular filtration rate; moreover, it is a well-established marker of cardiovascular events (5,6).

At present, guidelines recommend screening of patients with newly detected AF with echocardiography to identify underlying structural pathologies and potential reversible causes of AF and to tailor treatments. There are a large number of reported echocardiographic measures of diastolic function, including left atrial size, that relate to stroke risk, but with little consensus as to how to simply and reliably incorporate these into risk assessment. However, for prediction of the risk of thromboembolic events, a complementary measurement of NT-proBNP is attractive as an easily available tool to provide further guidance on management.

*Ziad Hijazi, MD, PhD
Christopher B. Granger, MD
Lars Wallentin, MD, PhD

*Uppsala Clinical Research Center
Uppsala University
Uppsala Science Park
Dag Hammarskjölds väg 14B, 1st Floor
Uppsala 75237
Sweden
E-mail: Ziad.Hijazi@ucr.uu.se

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